THROMBOTIC MICROANGIOPATHIES
AKI

By

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Agenda

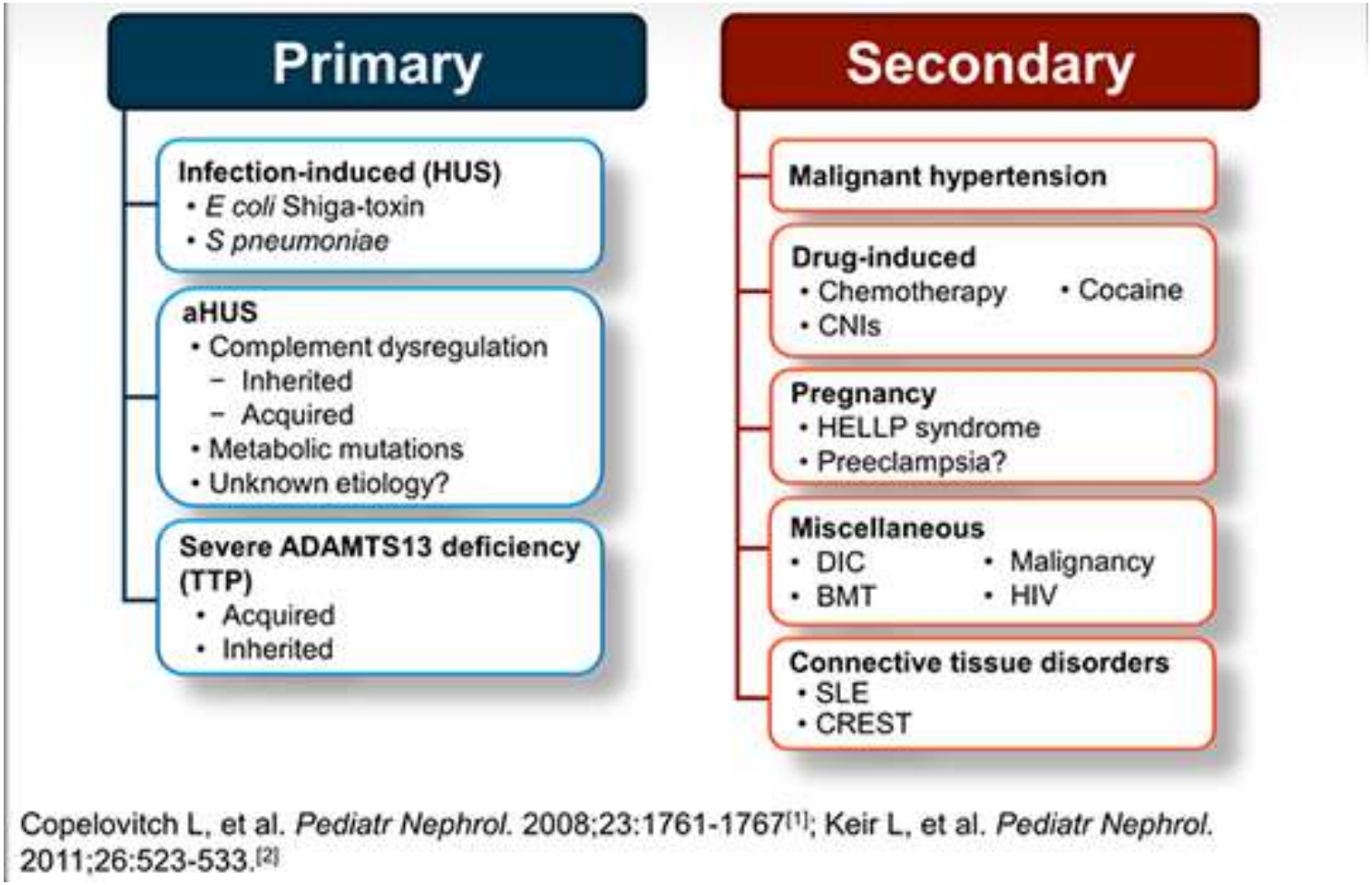
- **Introduction**
- **Magnitude of the problem**
- **When to suspect ??**
- **Approach to diagnosis and management**

Introduction

- Intra-luminal **platelet** thrombosis
- **Capillaries, arterioles**
- Due to **endothelial injury**
- Results in

  - **Consumption of platelets**
  - **MAHA**
  - **Partial or complete obstruction of vs lumina**

MAHA + Thrombocytopenia



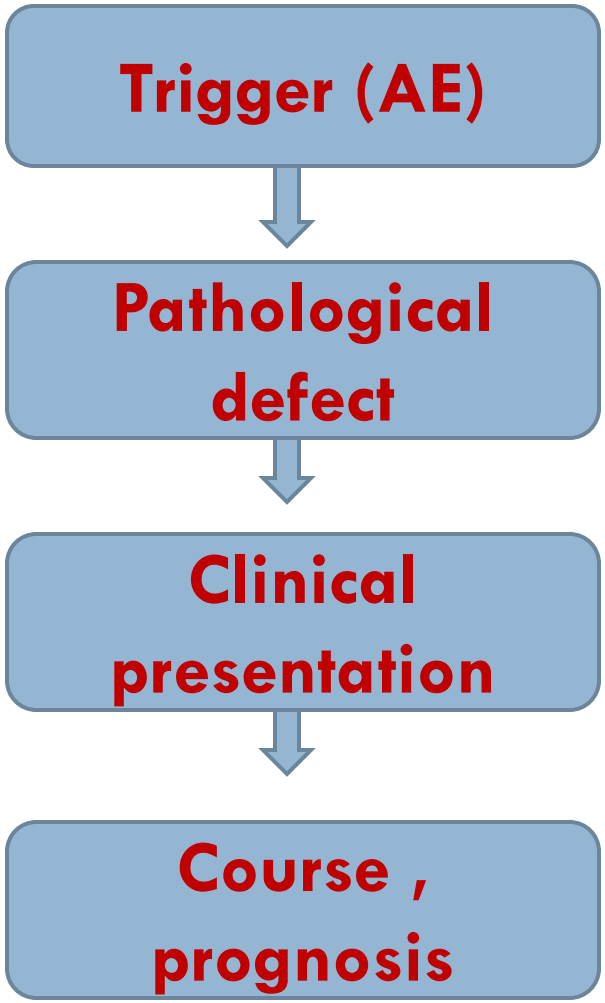
Copelovitch L, et al. *Pediatr Nephrol.* 2008;23:1761-1767[1]; Keir L, et al. *Pediatr Nephrol.* 2011;26:523-533.[2]

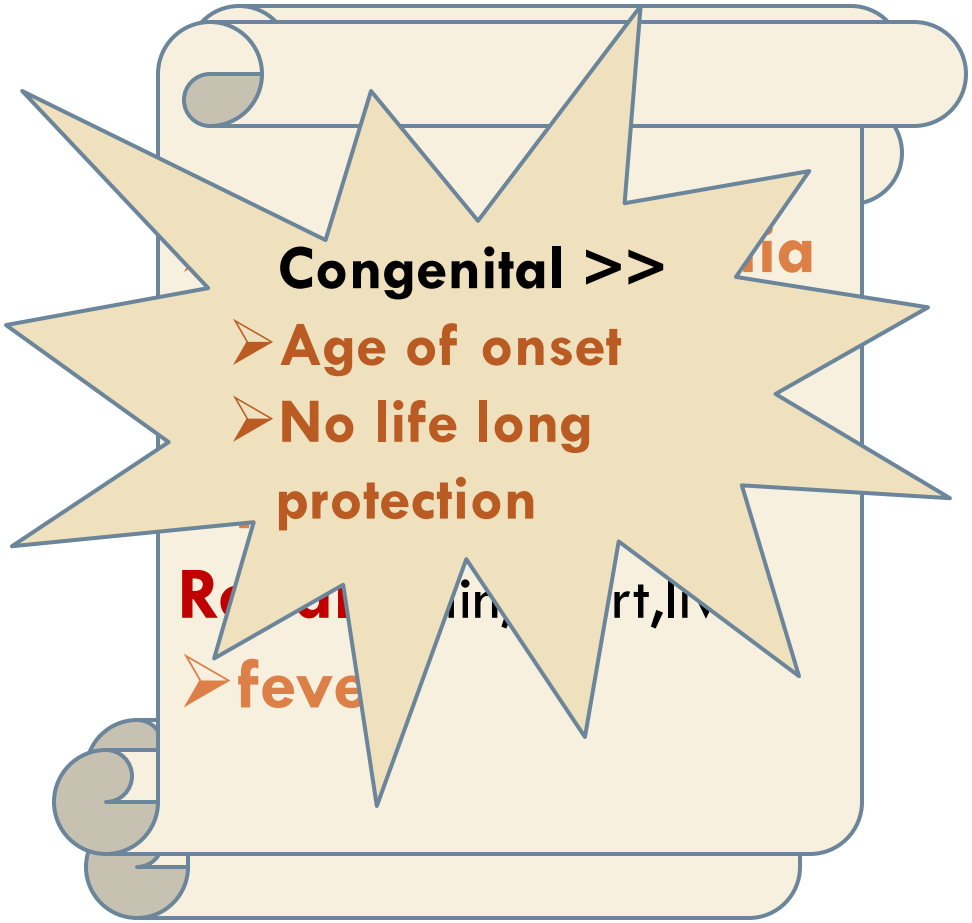
Magnitude of the problem

It is the time of extra-ordinary diversity to begin

- New born – Elderly
- Hereditary – Acquired
- Asymptomatic – lethal
- Renal-CNS-GIT-Skin-Pancreas
- Acute- recurring- chronic
- Amenable- treatment resistant

Generally (when to suspect ??)





Focus on

- **Shiga toxin HUS (STEC-HUS)**
- **Neuraminidase HUS**
- **Atypical HUS (aHUS)**
- **Thrombotic thrombocytopenic purpura (TTP)**

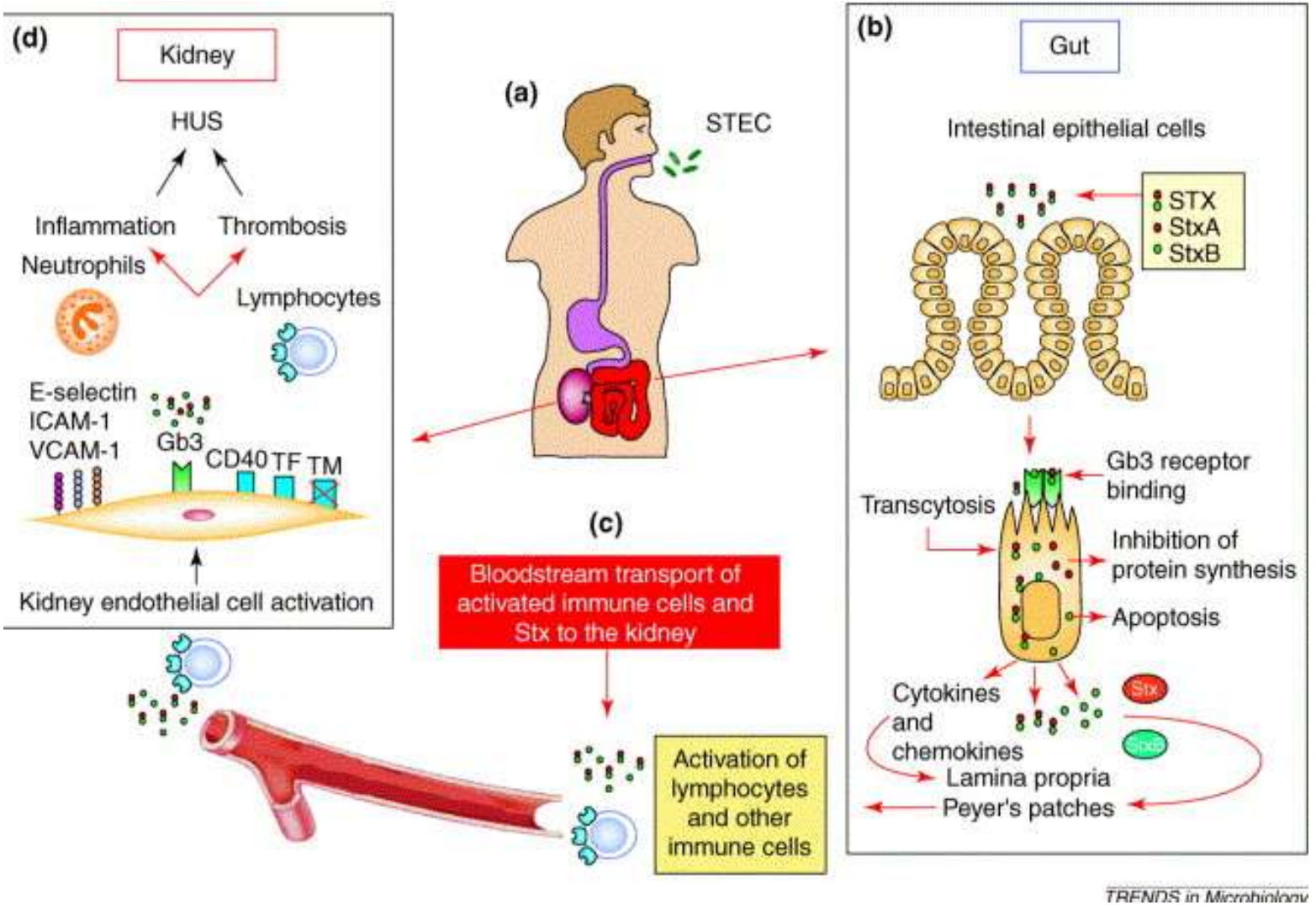
Shiga toxin HUS (STEC-HUS)

Trigger (AE)

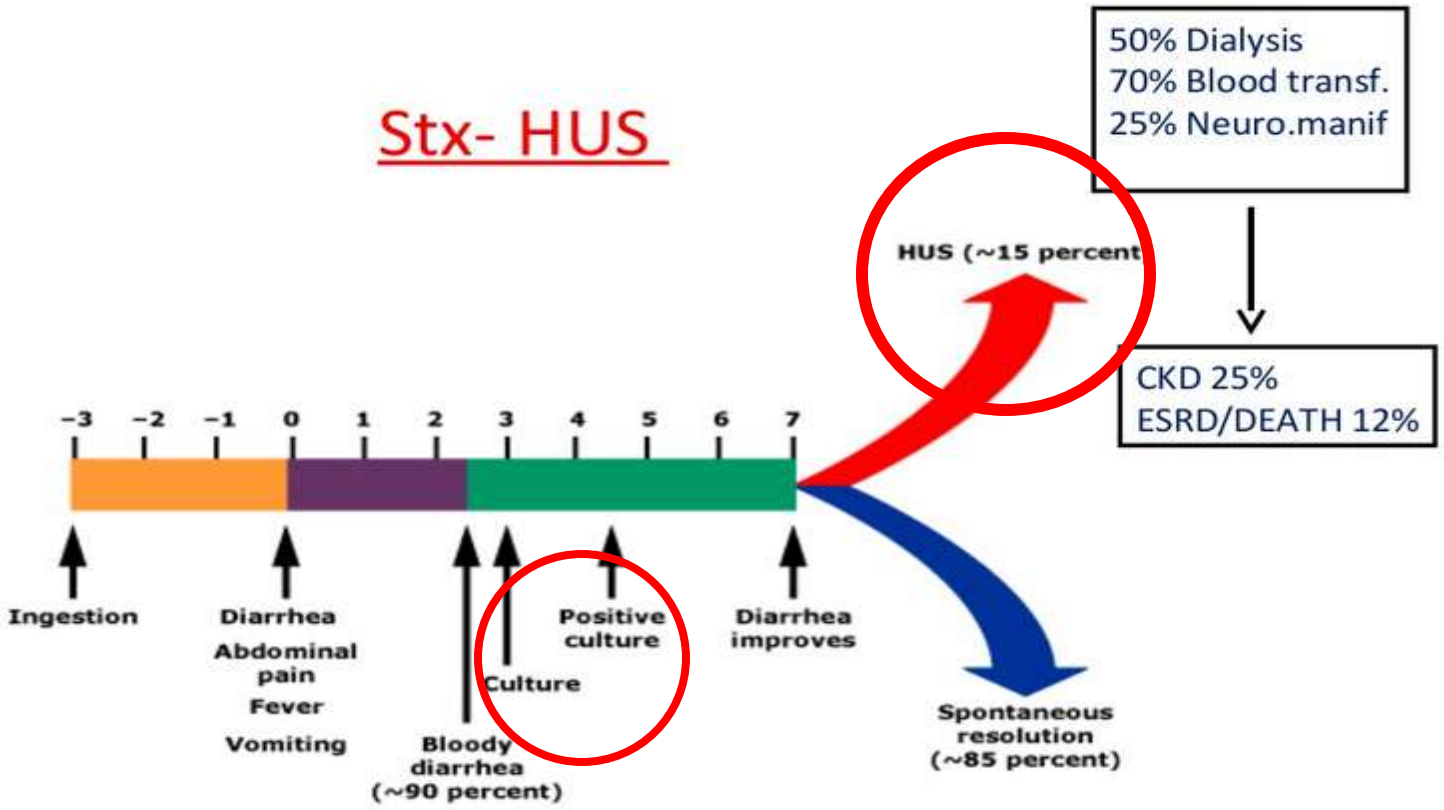
- Shiga toxin producing E.coli with many serotypes :
  O157:H7- O104:H4
- S.dysenteriae

- **Stool culture**
- **Antibody to O157 in convalescence**

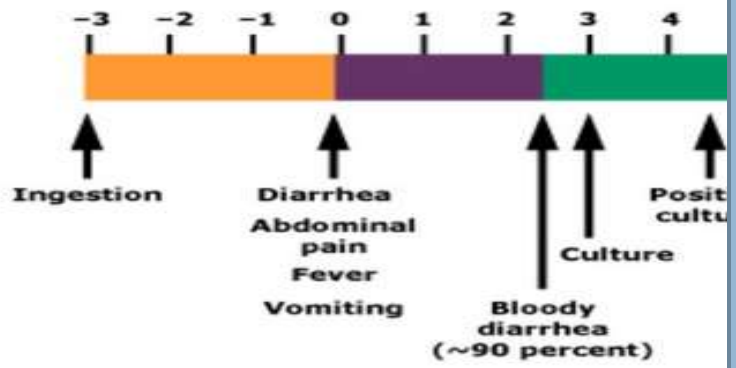
Pathogenesis



Clinical course, consequences



Management



- **Volume rehydration by isotonic saline**
- **Avoid anti-motility agents**
- **Bowel rest in bloody diarrhea**

- **Antibiotics should be reserved to bactremia, shigella dysentry not for GE**
  - ✓Quinolones,trimethoprime>> increase STX gene expression
  - ✓Azithromycin (German outbreak)
- **PEX** :
  - ✓no RCTs
  - ✓Improve MR
  - ✓Should be considered in adult patient with severe AKI or CNS involvement
- **Transplantation** : low recurrence rate

2011 data

The Journal of Immunology

This information is current as of February 9, 2015.

Alternative Pathway Activation of Complement by Shiga Toxin Promotes Exuberant C3a Formation That Triggers Microvascular Thrombosis

Marina Morigi, Miriam Galbusera, Sara Gastoldi, Monica Locatelli, Simona Buelli, Anna Pezzotta, Chiara Pagani, Marina Noris, Marco Gobbi, Matteo Stravalaci, Daniela Rottoli, Francesco Tedesco, Giuseppe Remuzzi and Carlamaria Zoja

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CORRESPONDENCE

Eculizumab in Severe Shiga-Toxin–Associated HUS

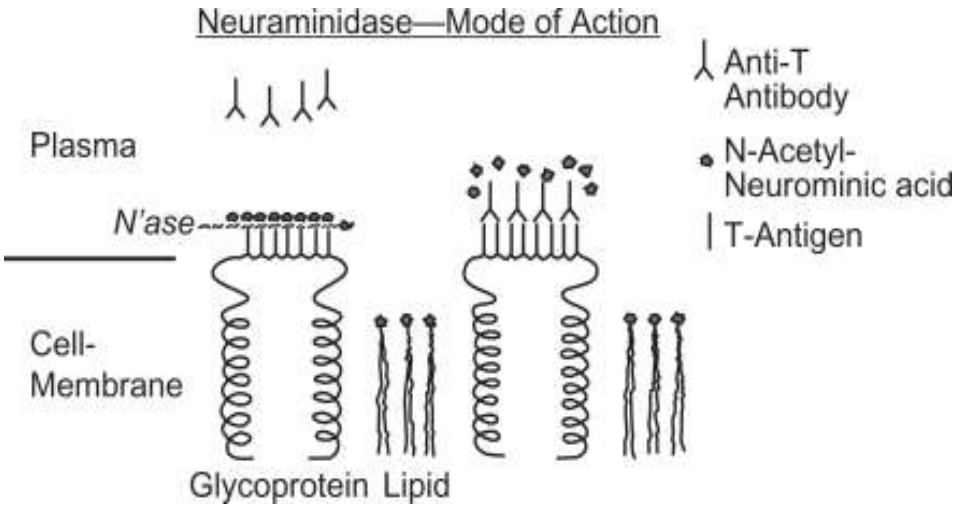
N Engl J Med 2011; 364:2561-2563 | June 30, 2011 | DOI: 10.1056/NEJMc1100859

High plasma levels of complement activation products Bb and C5b-9 were measured in children with STEC-HUS

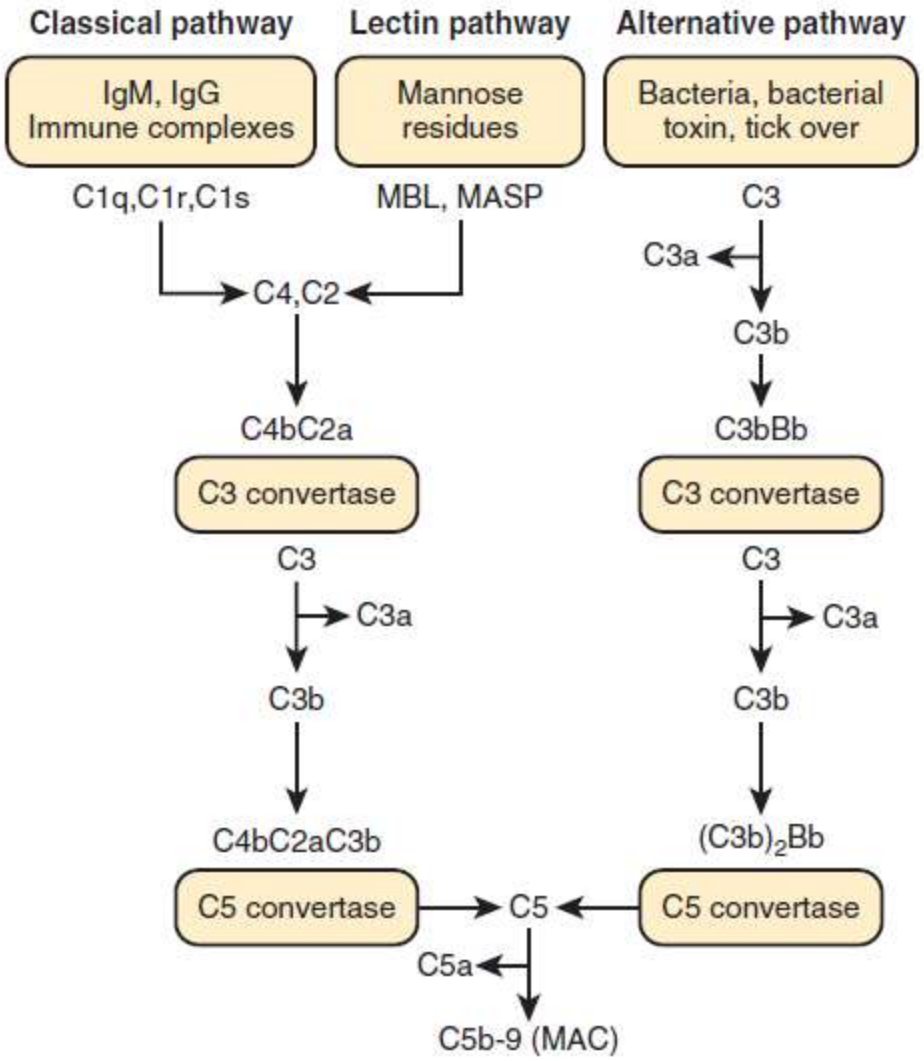
Need more RCTs

Neuraminidase HUS

- Post s.pneumoniae pneumonia or meningitis
- Rare , fatal
- MR 25%
- **Coombs +ve**
- Management:
  - **Antibiotics**
  - PEX aggravate problem (may be combined with steroid)



Atypical HUS (aHUS)



Complement alternative ay

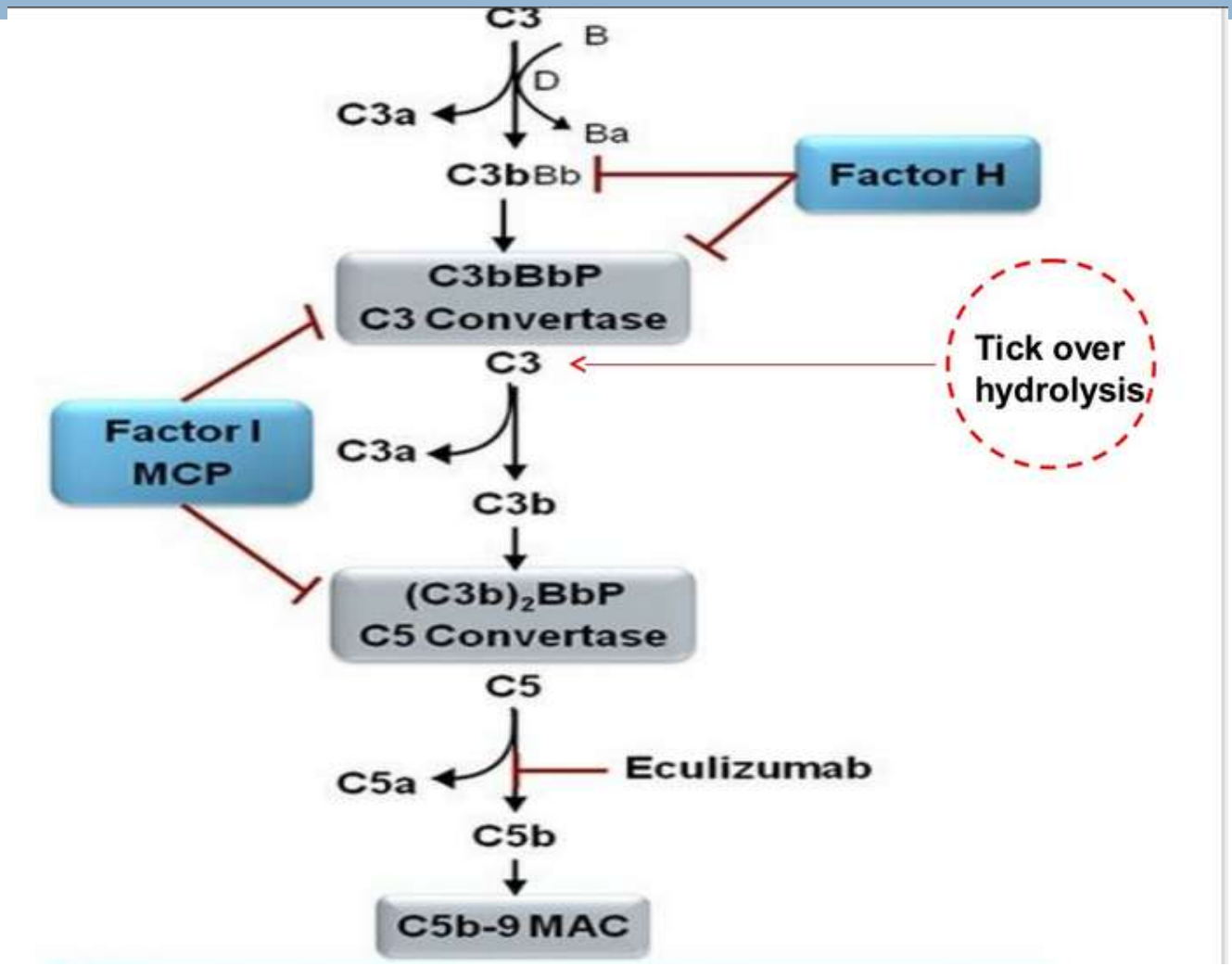
Low C3 normal C4

plement gene mutation carriers

ing factors

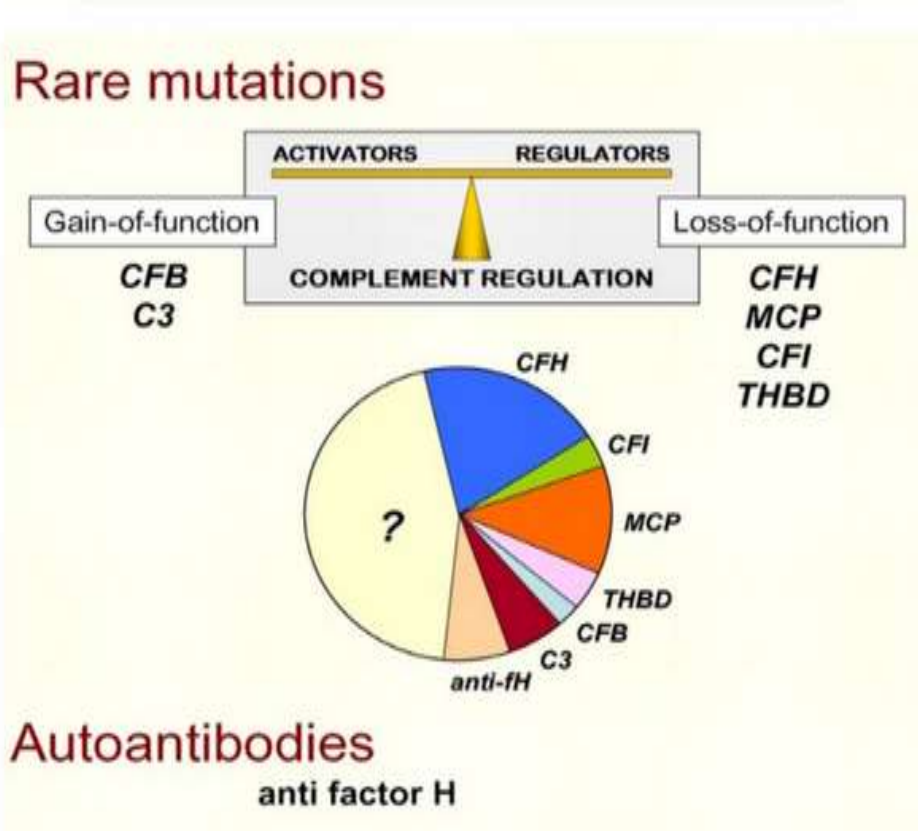
Infection, immunosuppressive drugs, cancer therapies, oral contraceptives, pregnancy, childbirth, etc.

Pathogenesis



Pathogenesis, cont.

- Variety **of genetic abnormalities in** members of **alternative** pathway of complement >> **60** %
- **Acquired (10%):** inhibitory antibodies

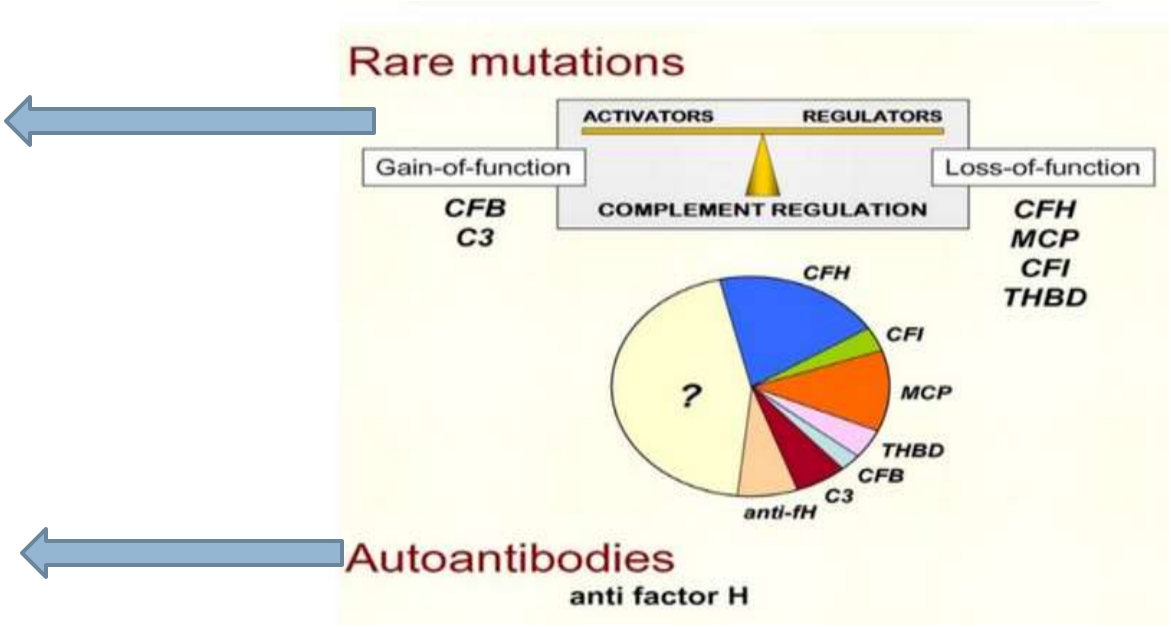


Pathogenesis, cont.

Outcome of Atypical Hemolytic Uremic Syndrome According to Associated Genetic Abnormality					
Affected Gene	**Affected Protein (Main Effect)**	**Frequency in aHUS (%)**	**Rate of Remission with Plasma Exchange* (%)**	**Mortality (5-10 yr) or ESRD (%)**	**Rate of Recurrence After Kidney Transplant (%)**
CFH	Factor H (no binding to endothelium)	30	60 (dose and timing dependent)	70-80	60-70
CFHL1, CFHL3	Factor HR1, R3 (anti–factor H antibodies)	5-10	70-80 (combined with immunosuppression)	30-40	40
MCP	Membrane cofactor protein (no surface expression)	10-15	No indication to plasma exchange	<20	15-20
CFI	Factor I (low levels/low cofactor action)	4-10	30-40	60-70	70-80
CFB	Factor B (C3 convertase stabilization)	1-2	30	70	One case reported
C3	Complement C3 (resistance to C3b inactivation)	8-10	40-50	60	40-50
THBD	Thrombomodulin (reduced C3b inactivation)	4-5	60	60	One case reported

Clinical course

- **Presented clinically in childhood (60%)**
- **Severe presentation**
- **Renal and extra renal**
- **Outcome according to mutation**



Management

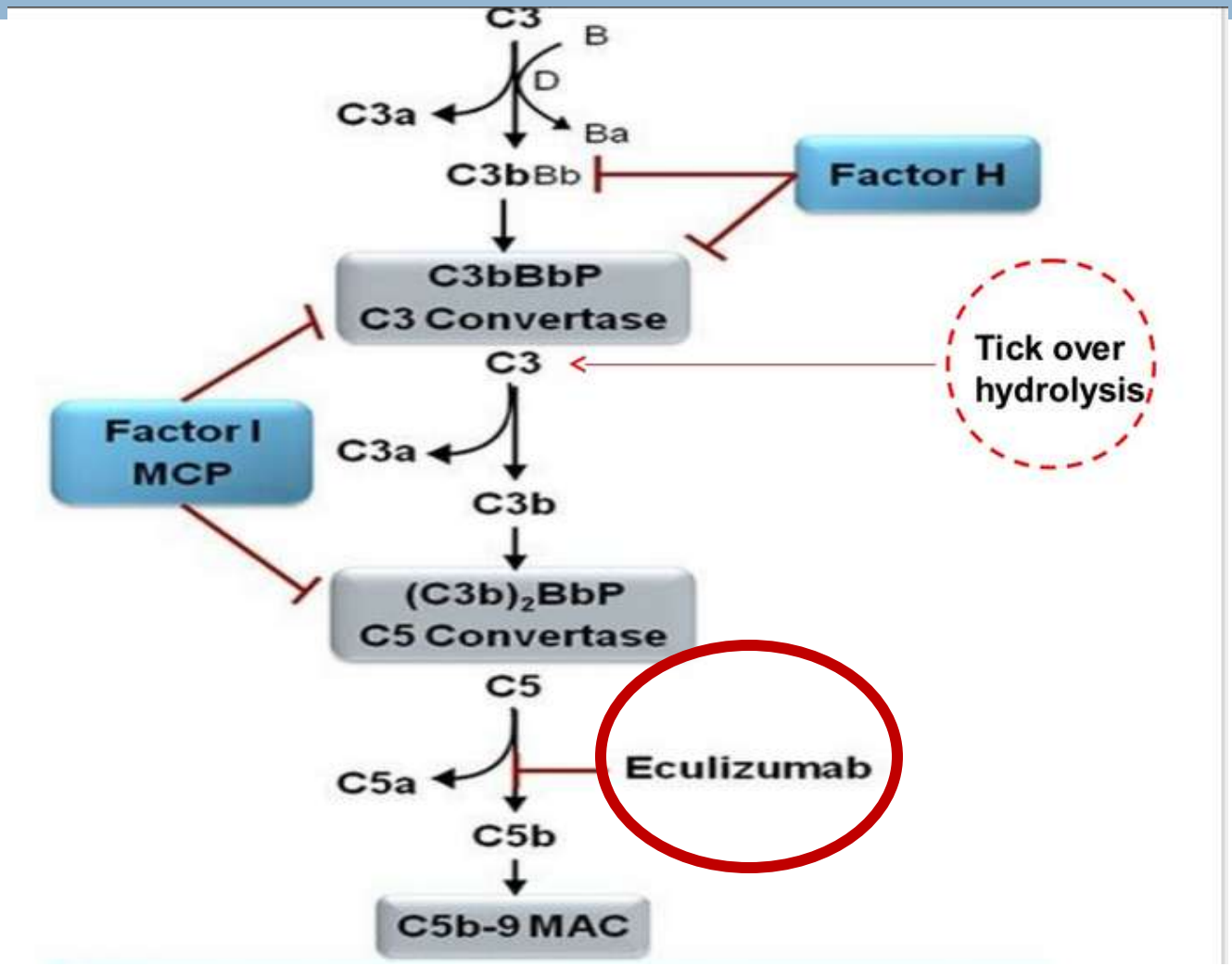
Plasma therapy

- **Plasma Exchange is superior to Infusion:** allows supplying larger amounts of plasma than would be possible with infusion while avoiding fluid overload.
- **1-2 PV/day**

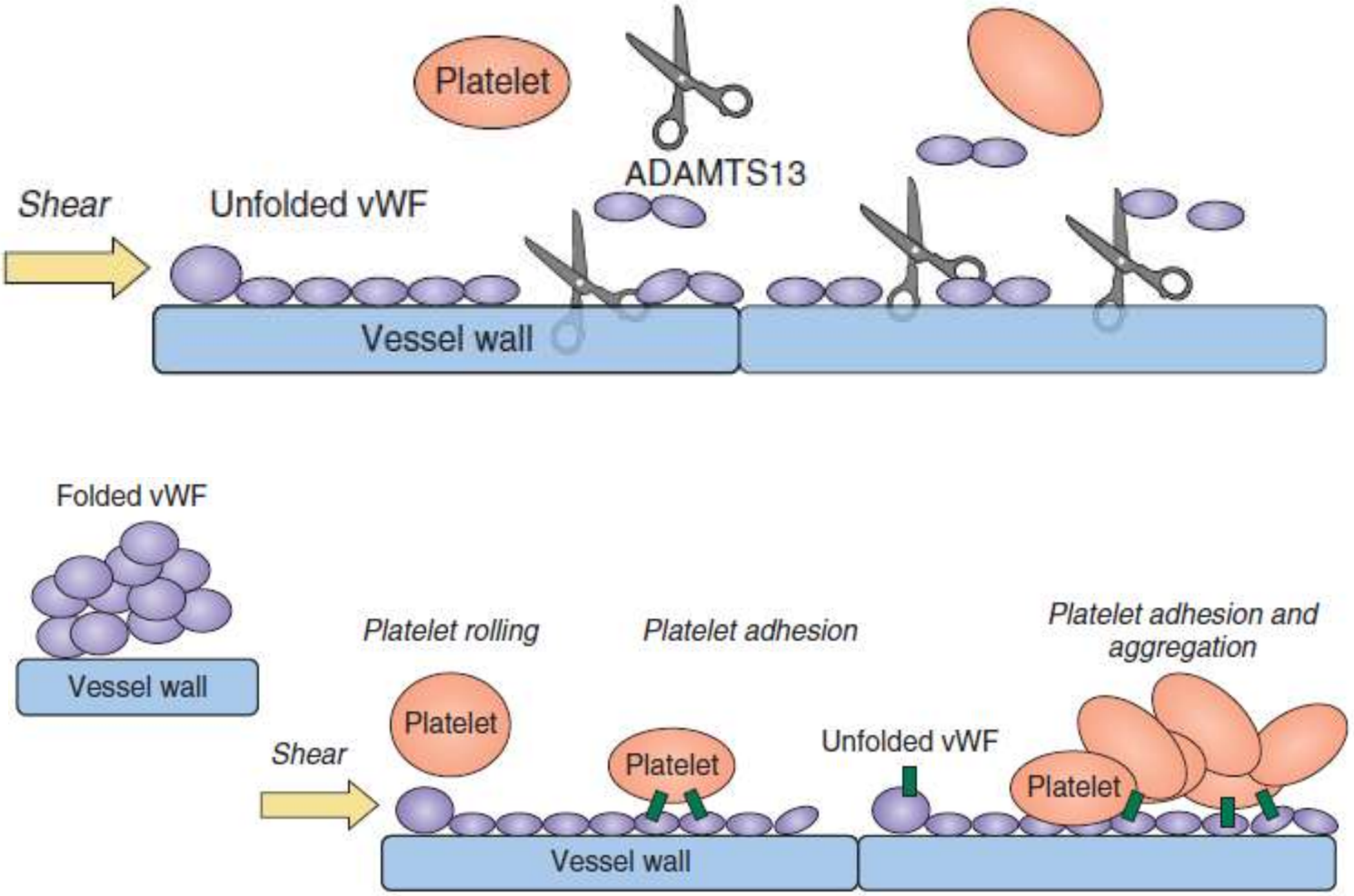
Immunosuppressives

- Corticosteroid, azathioprine or MMF combined with plasma exchange allowed long-term dialysis-free survival in 60% to 70% of patients.
- FFP+corticosteroid : if antibody detected

Management, cont.



TTP (Deficient ADAMTS13)



(Deficient ADAMTS13)

Acquired (Auto-antibody)

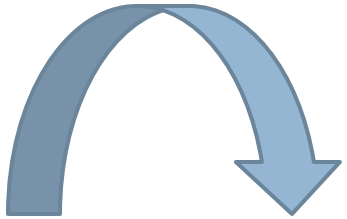
- 60-90%
- Severe deficiency

Genetic mutation

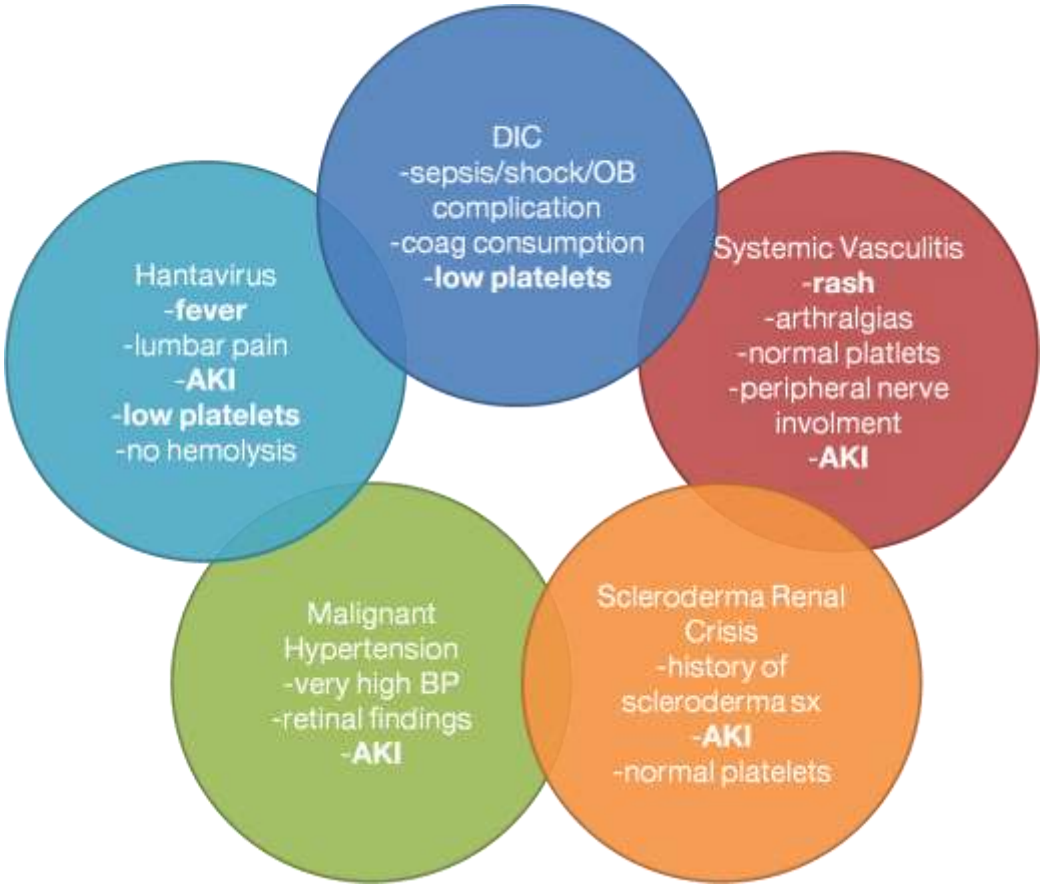
- Rare
- More than 120 mutations uptill now

Clinical course, presentation

- **Classical pentad (rare)**
  - Thrombocytopenia
  - MAHA
  - Fluctuating neurological signs
  - AKI
  - Fever
- **TTP/HUS**
  - Thrombocytopenia
  - MAHA



Cont.



ADAMTS13 testing

Less than 5%

IgG

Exclusion of infection or drugs

Management

- **Plasma exchange** :1-2 PV till improvement or platelet count >150000 (corner stone) as:
  - **Replace protease activity.**
  - **Rapid removing anti-ADAMTS 13 Abs (Advantage over infusion).**
- **FFP,Cryosupernatent**
- **Corticosteroids in combination with PEX**
- **Rituximab**
  - **Anti-CD20 monoclonal antibody depleting B lymphocytes**
  - **For resistant cases (PEX+methylprednisolone)**
  - **Prophylactic in recurrence or presence of antibodies**
  - **Significant success rate (95%) – 1-4 weeks after dose administration**
  - **Relapse 9m-4yr >> 10%**
  - **Should be monitored by ADAMTS 13 , Antibody titre testing.**

Management, cont.

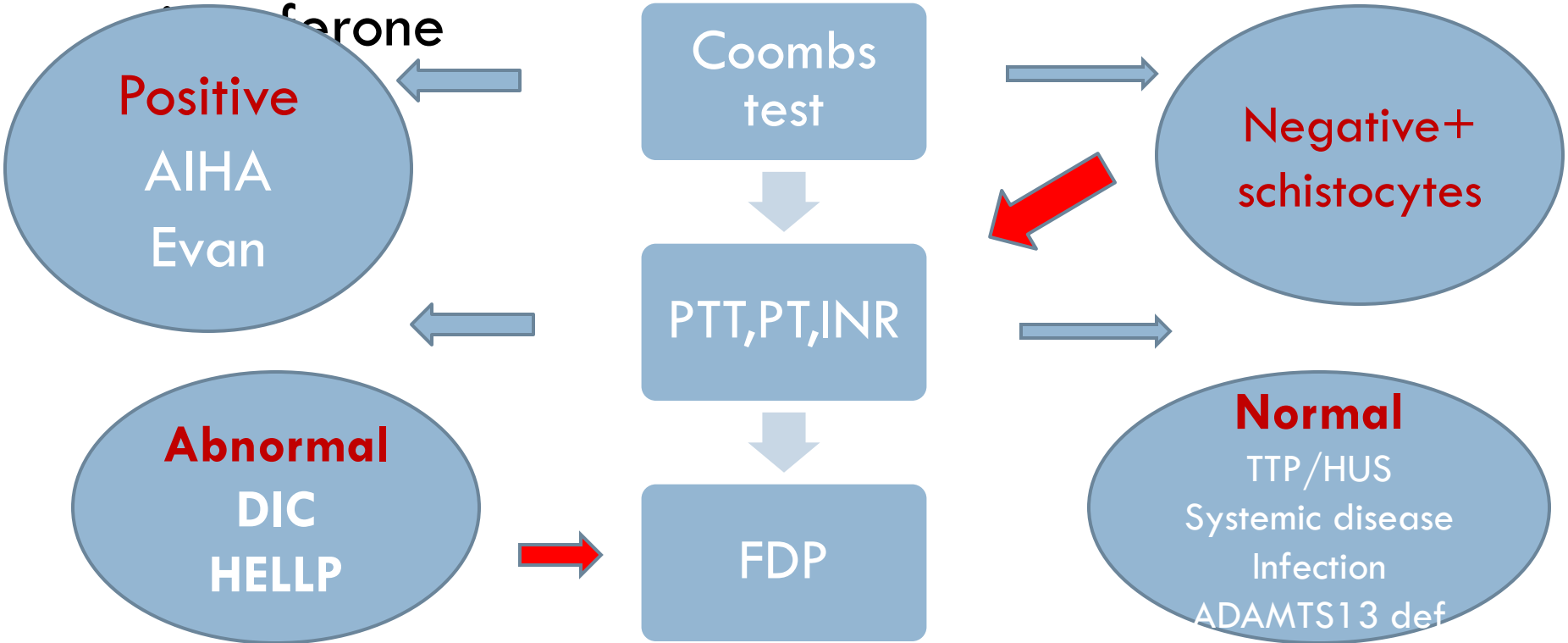
- Patients with congenital ADAMTS 13 deficiency who are :
  - Frequent relapser
  - With severe clinical renal,neurological manifestations
  - With sibling died from TTP

Prophylactic plasma infusion every 2 to 3 weeks

Diagnostic Approach

Anemia – thrombocytopenia-reticulocytosis-increased bilirubin,LDH

Exclude Drug induced: quinine-simvastatin-CNIs-



> The task of the modern educator is not to cut down jungles, but to irrigate deserts.
>
> **C. S. Lewis**

THANKS